Mechanisms of Insulin Resistance Following Injury

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To assess the mechanisms of insulin resistance following injury, we examined the relationship between insulin levels and glucose disposal in nine nonseptic, multiple trauma patients (average age 32 years, Injury Severity Score 22) five to 13 days postinjury. Fourteen age-matched normals served as controls. Using a modification of the euglycemic insulin clamp technique, insulin was infused in 35 two-hour studies using at least one of four infusion rates (0.5, 1.0, 2.0 or 5.0 mU/kg min). Basal glucose levels were maintained by a variable infusion of 20% dextrose using bedside glucose monitoring and a servo-control algorithm. The amount of glucose infused reflected glucose disposal (M, mg/kg · min). Tracer doses of (6,6,$^2D_2$) glucose were administered in selected subjects to determine endogenous glucose production. At plasma insulin concentrations less than 100 μU/ml, responses in both groups were similar. However, maximal glucose disposal rates were significantly less in the patients than in the controls (9.17 ± 0.87 mg/kg · min *vs.* 14.3 ± 0.78, mean ± SEM, $p < 0.01$). Insulin clearance rates in the patients were almost twice that seen in controls. To further characterize this decrease in insulin responsiveness, we studied six additional patients and 12 controls following the acute elevation of glucose 125 mg/dl above basal (hyperglycemic glucose clamp). In spite of exaggerated endogenous insulin production in the patients (80–200 μU/ml *vs.* 30–70 in controls), M was significantly lower (6.23 ± 0.59 *vs.* 9.46 ± 0.79, $p < 0.02$). In conclusion, this study demonstrated that (1) the maximal rate of glucose disposal is reduced in trauma patients; (2) the metabolic clearance rate of insulin in the injured patients is almost twice normal and; (3) insulin resistance following injury appears to occur in peripheral tissues, probably skeletal muscle, and is consistent with a postreceptor defect.

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HYPERGLYCEMIA AND GLUCOSE intolerance are frequent manifestations of the metabolic response to surgical illness. Oral and intravenous glucose tolerance tests following injury,[1,2] burn shock,[3,4] or systemic infection[5,6] demonstrate delayed disposal of glucose from plasma into body tissues. This apparent "stress diabetes" or "diabetes of injury" would be readily explained if an insulin deficiency existed. In fact Allison and associates,[3] Carey et al.,[1] and Wilmore and coworkers[7] demonstrated that during the early or "ebb" phase of injury, insulin concentrations were decreased even in the face of hyperglycemia.

Following resuscitation, as the trauma patient enters the "flow" phase of injury, beta cell responsiveness to glucose administration returns and plasma insulin concentration is appropriate or even higher than expected following a glucose load.[3,7] Despite this appropriate acute insulin response in injured patients to an intravenous glucose load, glucose intolerance and hyperglycemia persisted, suggesting that certain target tissues of the injured patient are relatively insensitive to the effects of circulating insulin.

Recent development of small portable glucose analysers which provide rapid results or on-line devices (*e.g.*, the artificial beta cell unit) which constantly monitor plasma glucose, allow bedside glucose monitoring and experiments which control one of the two variables (insulin or glucose concentration). The biologic response of the other, or dependent variable, can thus be described more precisely. The hyperglycemic glucose clamp technique[8] acutely elevates plasma glucose 125 mg/dl above basal and examines the individual's insulin response to fixed hyperglycemia. This technique also allows quantitation of tissue disposal of glucose. In the euglycemic insulin clamp[8] exogenous insulin is infused at a fixed rate to increase plasma insulin concentration and maintain it at a constant level. A variable speed infusion pump is frequently adjusted to deliver glucose at a rate that maintains euglycemia and prevents hypoglycemia. Hence, glucose disposal is primarily dependent upon the dose of exogenous insulin administered. By infusing insulin at varying rates, dose-response curves may be constructed, defining the relationship between glucose disposal and plasma insulin concentration.

Presented at the Annual Meeting of the American Surgical Association, Boston, Massachusetts, April 21–23, 1982.

Supported by: NIH Trauma Center Grant #NIGM P50 GM 29327-01 and a grant from the Grace Foundation, New York, NY.

* Recipient of a grant for Advanced Training in Surgical Oncology #CA09280.

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0003-4932/82/1000/0420 $01.60

These curves aid in understanding altered glucose disposal and characterize insulin resistance. The first step in insulin-mediated, facilitated glucose uptake is the binding of insulin to receptors located on the cell membrane of the target tissues. If a disease process is associated with a reduction in the number of insulin receptors, insulin resistance is manifest. Since an excess of receptors is normally found on target tissues, this defect may be overcome by simply administering more insulin, that is, if a prereceptor defect is present, supraphysiologic insulin doses should elicit a normal response.[9,10] Insulin also plays a critical role in regulating intracellular metabolism once glucose has crossed the cell membrane.[11] Alterations in normal intracellular glucose metabolism may also produce insulin resistance. In this situation, a postreceptor defect, a normal response cannot be elicited, administering large doses of insulin to increase plasma insulin concentration[9] (see Appendix).

In this study we have utilized the euglycemic insulin clamp technique[8] to construct dose-response curves and thereby characterize the relationship between insulin and glucose disposal in normals and injured patients. In addition, we have used the hyperglycemic glucose clamp technique[8] in both groups to mimic the clinical situation during glucose infusion and to quantitate glucose disposal during combined hyperglycemia and hyperinsulinemia.

Materials and Methods

Subjects

Controls. Seventeen healthy, male volunteers ranging in age from 21 to 42 (mean ± SEM 29 ± 2) years served as control subjects. All except one were within 10% of their ideal body weight (Metropolitan Life Insurance Company tables). The exception was a nonobese weightlifter who weighed 111 kg. None took any medications or had family histories of diabetes mellitus. All consumed weight-maintaining *ad lib* diets containing at least 200–300 grams of carbohydrates per day, and this intake was assured for at least three days prior to the study. Eleven of the volunteers were studied using both the insulin and glucose clamp techniques. Three were studied using only the glucose clamp technique, and an additional three subjects were studied using the euglycemic insulin clamp.

Patients. Fifteen patients (14 males and one female) admitted to the Burn/Trauma Unit of the Brigham and Women's Hospital with acute injuries were studied. They ranged in age from 19 to 51 (mean 29 ± 2) years. All were within 10% of their ideal body weight prior to their injury. All were previously healthy before injury, and none took medications. None had family histories of diabetes mellitus. Those patients who required surgical procedures during the early phase of their injury were studied at least three days following operation. All patients were hemodynamically stable and had normal electolytes, pH, blood volume, and urinary output at the time of their study. None were infected previously or at the time of study as determined by clinical signs and symptoms, leukocyte counts, body temperatures, and chest roentgenograms. None had positive bloodstream cultures before or at the time of study. All patients received at least 200–300 grams of carbohydrates either enterally or intravenously for at least two to three days prior to being studied. Most patients received vigorous nutritional support prior to study.

Nine of the 15 patients were studied five to 14 days following injury, using the euglycemic insulin clamp. The patients in this group had a mean age of 32 ± 3 (range 19–51) years. Five sustained multiple injuries resulting from motor vehicle accidents, and four had body surface burns (Table 1). The mean Injury Severity Score (ISS)[12] for these patients was 22 ± 2 (range 9–32). The remaining six patients were studied five to 13 days following injury using the hyperglycemic glucose clamp technique. The mean age in these six patients was 25 ± 1 (range 22–30) years. Four of these patients had multiple injuries secondary to motor vehicle accidents, and two patients had large surface area burns. The mean ISS for the glucose clamp patients was 26 ± 5 (range 9–45) (Table 2). All of the patients survived their injuries.

The experimental protocol was approved by the Committee on Human Subjects of the Brigham and Women's Hospital. Prior to participation the nature, purpose, and risks of the study were explained in detail to all subjects and/or their relatives in the presence of a patient advocate, and informed consent was obtained.

Experimental Protocol

All studies were begun between 6 and 7 am. The volunteers were studied after a 10 to 12-hour overnight fast. All patients were fasted and received glucose-free intravenous solutions for at least six hours before study to maintain a normal state of hydration. In the controls a Teflon® catheter was placed in an antecubital vein for the infusion of all solutions. An additional catheter was placed into a dorsal hand vein in order to obtain arterialized venous samples using the heated hand technique.[13] Whenever possible, existing intravenous catheters were used for infusing solutions in the patient group. If a patient had an arterial catheter in place for clinical monitoring, arterial samples were obtained from this site. In some patients, however, catheters as described above were required. The subjects rested for 30 to 60 minutes following venipuncture to achieve a resting basal state before starting the study.

TABLE 1. *Description of Patients—Insulin Clamp*

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	BSA (m^2)	Injury	Injury Severity Score	Days after Injury	Days Postop
A	23	M	182.9	89.6	2.12	Open fracture left clavicle, fracture first rib, fracture left mandible	9	5	5
B	30	M	145.2	65.7	1.57	20% total body surface burn, cerebral ischemia, smoke inhalation	25	5	—
C	37	M	149.6	73.6	1.69	40% total body surface burn	16	14	3
D	19	M	154.0	60.6	1.58	Ruptured spleen, open patellar fracture	25	5	5
E	24	M	158.4	66.0	1.68	Bilateral pneumothorax (right tension pneumothorax), multiple rib fractures, pulmonary contusion	29	5	—
F	41	M	154.0	75.1	1.74	50% total body surface burn	25	6	—
G	37	M	182.9	79.5	2.01	Fracture, dislocation left pelvis, left sciatic nerve injury, postdislocation of right knee, right malleolar fracture, blunt laryngeal trauma	32	5	—
H	51	M	180.3	82.5	2.03	40% total body surface burn, smoke inhalation	16	7	—
I	27	M	167.6	74.4	1.84	Crush injury left leg, left fibula fracture, postdislocation of left knee, popliteal artery avulsion.	18	8	6

Euglycemic insulin clamp. The responses to graded changes in plasma insulin concentrations were determined using the euglycemic insulin clamp technique in studies lasting two or four hours as previously described.[8,14] In the two-hour studies samples were taken to measure basal plasma glucose and basal plasma in-

TABLE 2. *Description of Patients—Glucose Clamp*

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	BSA (m^2)	Injury	Injury Severity Score	Days After Injury	Days Postop
A	29	M	177.8	70.0	1.87	Fractured spleen, femoral fracture, multiple rib fractures, hemopneumothorax	34	5	5
B	24	M	182.9	75.8	1.97	60% total body surface burn	25	6	3
C	22	M	167.6	61.0	1.69	Pelvic fractures, multiple rib fractures, lung contusion	19	7	3
D	24	M	177.8	75.0	1.93	Pelvic fracture, retroperitoneal hemorrhage, head trauma	22	7	—
E	30	F	152.4	60.5	1.57	70% total body surface burn, unstable T_{10} fracture	45	13	10
F	22	M	175.3	77.3	1.93	Multiple long-bone fractures	9	6	3

sulin and a priming dose of crystalline porcine insulin was infused over a ten-minute period. Thereafter a constant infusion of insulin was utilized to maintain a fixed elevated plasma insulin concentration throughout the study. Plasma glucose was measured at the bedside every ten minutes throughout the study using a glucose analyser, and euglycemia was maintained by a variable infusion of 20% dextrose. The rate of dextrose infusion for each ten-minute period was calculated on a microcomputer (Apple II+, Apple Computer Company, Cupertino, CA) using a negative feedback algorithm.[8] In selected subjects the insulin infusion rate was increased after the initial 120-minute study period to achieve a higher plasma insulin concentration. This new plasma insulin level was maintained for an additional two hours. Prior to increasing the insulin infusion rate, a priming intravenous bolus of insulin was administered according to the following formula[14]:

$$\text{insulin bolus (mU)} = \text{distribution volume (100 ml/kg} \times \text{body wgt in kg)} \times \text{desired increment in plasma insulin concentration } (\mu\text{U/ml}) \div 1000$$

In addition to measuring plasma glucose concentration every ten minutes, we obtained samples every 20 minutes for plasma insulin determinations.

In the control group 10 subjects were studied for two hours at an infusion rate of 1.0 mU/kg · min. A total of six volunteers were studied for four hours with the following infusion rates: 0.5 to 2.0 mU/kg · min (two subjects), 0.5 to 5.0 mU/kg · min (two subjects), and 2.0 to 5.0 mU/kg · min (two subjects).

Five patients were studied for two hours. The insulin infusion rate in three was 1.0 mU/kg · min, and the infusion rate was 5.0 mU/kg · min in the remaining two patients. Four patients were studied for four hours. Three initially received insulin at 1.0 mU/kg · min which was subsequently increased to 2.0 mU/kg · min after 120 minutes. One patients's insulin infusion rate was begun at 2.0 mU/kg · min and increased to 5.0 mU/kg · min.

Thus, in the control group there were ten studies at an insulin infusion rate of 1.0 mU/kg · min and four each at 0.05, 2.0 and 5.0 mU/kg · min. Among the patients there were six studies at 1.0 mU/kg · min, four at 2.0 mU/kg · min, and three studies at 5.0 mU/kg · min.

Hyperglycemic glucose clamp. The hyperglycemic glucose clamp technique[8] was utilized to assess insulin response to fixed hyperglycemia. After samples were taken to measure basal plasma glucose, insulin, and glucagon, a 14-minute priming infusion of 20% dextrose was given to acutely elevate the plasma glucose concentration 125 mg/dl above basal. Plasma glucose was then measured every ten minutes, and these values were utilized, employing a negative feedback principal,[8] to calculate the infusion rate necessary to maintain fixed hyperglycemia at the desired level for the following ten-min interval. In addition, blood samples were obtained every 20 minutes for the determination of plasma insulin and glucagon. Urine samples were taken prior to infusing dextrose, and all urine produced during the two-hour study period was collected and analysed for glucose to calculate urinary glucose losses. Twelve volunteers and six patients were studied using this technique.

Isotopic infusions. In two patients undergoing the hyperglycemic glucose clamp, and one patient studied using the euglycemic clamp technique, (6,6$^2D_2$)-glucose was infused using a primed-constant infusion to determine the rate of endogenous glucose production and the extent of suppression during the clamp period. Following placement of the intravenous infusion catheter, a primed-constant infusion was begun and continued for two hours. The isotope infusion rate was 0.183 cc/minute, and the concentration of the infusate was calculated to achieve approximately 1.15 atom per cent excess (APE) in all subjects. The prime to infusion rate was 80:1. Blood samples were obtained at 90, 100 110, and 120 minutes after priming for determination of basal glucose production. At the end of two hours the insulin or glucose clamp was begun. Glucose turnover was determined during the two hours of the clamp by maintaining the constant infusion and adding additional isotope to the 20% dextrose to obtain approximately 0.65 APE. The rationale for adding isotope to the glucose infusion was to avoid rapid changes in the enrichment of plasma glucose during the clamp procedure. The general principles of this approach were first described by Hetenyi and Wrenshall.[15] During the clamp blood samples were obtained every 10 minutes for isotope analysis.

Analytical Procedures

Plasma and urinary glucose was measured in duplicate using the glucose oxidase method on a Glucose Analyser II (Beckmann Instruments, Inc., Fullerton, CA). Plasma immunoreactive insulin was determined by radioimmunoassay as described by Soeldner et al.[16] Plasma glucagon was measured by radioimmunoassay using the technique of Unger and associates.[17] Plasma enrichment was determined using a gas chromatograph mass spectrometer (Hewlett–Packard, Model 5985B, Hewlett–Packard, Palo Alto, CA) as previously described.[18]

Data Analysis

The amount of glucose infused was calculated for each ten-minute interval throughout all experiments. Because

of the steady-state plasma glucose concentrations, this value approximates the total quantity of glucose removed from the plasma (M, mg/kg · minute) and reflects the rate of glucose disposal under the study conditions (see Appendix). Because compartmental analysis has shown that insulin's action is dependent upon the insulin concentration in a slowly equilibrating compartment and that equilibration between this compartment and plasma insulin concentration takes approximately 80 minutes,[19] the mean plasma insulin concentration for the last 50 minutes of each 120 study period was used for calculating the response during the euglycemic insulin clamp studies. Because the quantitation of glucose removal during equilibrium was desired, the mean glucose removal for each study was defined as the average glucose infusion rate over the last 50 minutes of each two-hour study. None of the subjects exhibited glucosuria during these studies, and no urinary correction was necessary. The Lineweaver–Burk transformation[20] was used to analyze the dose response curves derived from this data in order to enhance the interpretation of glucose kinetics.

The rate of insulin infusion was constant in these studies. Therefore, during the steady-state, the metabolic clearance rate of plasma insulin (MCR_I, ml/min · m^2) was calculated by:

$$MCR_I = \frac{\text{insulin infusion rate}}{\text{increase in plasma insulin concentration above basal}}$$

The computation for the MCR_I is based upon the assumption that basal insulin secretion is unchanged by insulin infusion. Determination of C-peptide concentrations during insulin infusion to achieve plasma concentrations of approximately 100 μU/ml show a 60% reduction. Thus, this calculation may overestimate MCR_I by 5–10%.[8]

The glucose infusion rate was calculated for each ten-minute interval during the hyperglycemic glucose clamp experiments as previously described.[8] Since each subject received a standardized infusion during the 14-minute priming period, the first 20 minutes of each study was not used, and glucose removal was calculated as the mean uptake for the last 100 minutes of each study. Urinary glucose losses were calculated for the study period, and this amount was subtracted from the mean glucose infusion rate to obtain M. The total plasma insulin concentration was defined as the mean of all the values obtained during the final 100 minutes of each study. Dividing M by the total insulin plasma insulin concentration (I) yields the M/I ratio, which reflects the quantity of glucose removed from the plasma per unit circulating insulin. This ratio serves as an index of tissue sensitivity to insulin.[8]

The deuterium in the sixth position is lost to water as glucose is resynthesized for 3-carbon precursors and thus cannot be recycled. It is, therefore, an appropriate tracer for measuring the rate of endogenous glucose production and the extent of suppression of production during the clamp period.[21] Calculations of glucose production were made using the Steele equation[22]: Ra = F/E in which Ra is the rate of glucose production (mg/kg · minute), F is the constant isotope infusion rate (mg/kg · min), and E is the enrichment of plasma glucose (APE). The calculation of endogenous glucose production using a primed-constant infusion as derived by Steele is optimized in steady-state conditions.[23] The hyperglycemic glucose and euglycemic insulin clamps utilize varying glucose infusion rates and although the plasma glucose remains constant, the glucose infusion rate changes every 10 min. By adding isotopically labeled glucose to 20% dextrose the marked swings in serum APE which would otherwise occur when unlabeled glucose was added have been minimized. Ra was then calculated[21] with a correction made for the additional isotope infused with the 20% dextrose. During the initial two hours of the primed-constant infusion, the total Ra of unlabeled glucose was entirely due to exogenous production. During the subsequent two-hour clamp study, however, total Ra was equal to the sum of endogenous production and exogenous infusion. Thus, endogenous production was calculated by subtracting the exogenous infusion from the total Ra determined via the Steele equation.

Statistical analysis. All data is expressed as the mean ± SEM. Paired and unpaired t-tests were used to test for statistical differences when appropriate. Linear regressions were calculated by the least squared method, and differences between curves were calculated using covariant analysis.

Results

Euglycemic Insulin Clamp

Fasting basal glucose in the patients (106 ± 3 mg/dl) was significantly increased above that in controls (98 ± 2, $p < 0.05$) even though mean basal insulin concentrations were comparable in the two groups (patients: 13 ± 1 μU/ml *vs.* controls 13 ± 2). In both groups plasma glucose was well maintained at basal levels throughout the period of insulin infusion (Fig. 1). The coefficients of variation of plasma glucose concentration during the study period when compared with basal was 2.7 ± 0.8% for the patients and 3.6 ± 0.6% for controls.

In the controls, plasma insulin levels achieved during insulin infusion were comparable with previous reports[8,14] and increased proportionally with the dose of insulin infused (Table 3). In contrast, insulin concen-

trations achieved during insulin infusion in the patients were consistently below levels observed in controls. The MCR_I was not altered by the dose of insulin infused in either group. At each insulin infusion rate MCR_I for the patients was consistently elevated above controls (Table 4). Taken as a group the MCR_I for the patients was 734 ± 52 ml/min · m^2, significantly greater than controls (497 ± 41, $p < 0.05$).

Glucose disposal in the patients was significantly decreased below control values at all doses of insulin infused (Table 3, Fig. 2). The rate of glucose disposal increased in both groups as a function of the plasma insulin concentrations achieved during the insulin infusions. The dose-response relationships, however, were significantly different between groups. At all plasma insulin concentrations, the controls demonstrated a significant increase in the quantity of glucose disposed when compared with the patients (Fig. 3). Increasing plasma insulin concentrations resulted in a glucose disposal response that approached a maximum, and Lineweaver–Burk transformation of the data (1/insulin concentration *vs.* 1/glucose disposal [M]) demonstrated a significant linear relationship between the variables. In the patients maximal glucose disposal was 9.17 ± 0.87 mg/kg · min, significantly lower than the 14.3 ± 0.78 mg/kg · min in the controls. In contrast, the plasma concentration of insulin required to achieve half-maximal response was comparable in both groups: 85 μU/ml in the patients and 86 in controls.

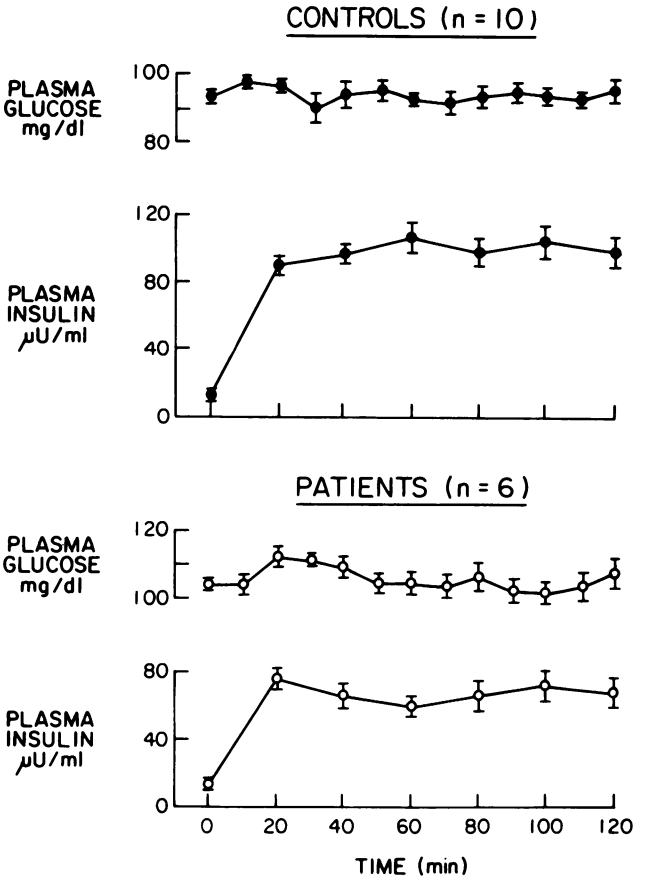

FIG. 1. Plasma glucose and insulin concentrations during euglycemic insulin clamp studies while infusing insulin at a rate of 1.0 mU/kg · min. Values represent mean ± SEM.

Hyperglycemic Glucose Clamp

The mean basal plasma glucose concentration in this patient group was 102 ± 5 mg/dl and 95 ± 3 in the controls (N.S.). Basal plasma insulin was 22 ± 5 μU/ml in the patients, significantly greater than the control value of 10 ± 1 μU/ml ($p < 0.005$). Mean basal plasma glucagons were 200 ± 50 pg/ml in the patients and 108 ± 22 in controls (N.S.). Both study groups were maintained at fixed hyperglycemia 125 mg/dl above basal (Fig. 4) and the coefficients of variation around the desired glucose concentration was $4.3 \pm 0.8\%$ for controls and $1.0 \pm 1.2\%$ for patients.

TABLE 3. *Glucose Removal (M) With Varying Insulin Infusion Rates*

			0.5 mU/kg · min.		1.0 mU/kg · min.		2.0 mU/kg · min.		5.0 mU/kg · min.	
Patient	Basal Glucose (mg/dl)	Basal Insulin (μU/ml)	M*	Plasma† Insulin	M	Plasma Insulin	M	Plasma Insulin	M	Plasma Insulin
A	89	13			3.10	82				
B	116	9			4.84	48				
C	104	13			3.58	51				
D	101	20			3.33	89	5.85	204		
E	102	14			3.19	68	8.20	159		
F	114	15			4.65	74	7.96	134		
G	100	13					5.64	114	7.63	304
H	113	9							7.20	233
I	119	12							9.01	295
Mean ± SEM	106 ± 3	13 ± 1			3.78 ± 0.31	69 ± 7	6.91 ± 0.68	153 ± 19	7.95 ± 0.55	277 ± 22
Controls	98 ± 2	13 ± 2	4.97 ± 0.67	53 ± 5	7.72 ± 0.57	89 ± 8	10.62 ± 1.31	200 ± 49	13.91 ± 0.99	628 ± 100

* mg/kg · min. † μU/ml.

TABLE 4. *Metabolic Clearance Rates of Insulin (ml/min • m²)*

Patient	1.0 mU/kg • min.	2.0 mU/kg • min.	5.0 mU/kg • min.
A	580	—	—
B	1081	—	—
C	1053	—	—
D	580	435	—
E	741	552	—
F	768	672	—
G	—	792	687
H	—	—	893
I	—	—	707
Mean ± SEM	801 ± 90	613 ± 77	762 ± 66
Control	569 ± 67	482 ± 98	360 ± 70

Mean plasma insulin concentration increased in both groups in response to fixed hyperglycemia and was significantly higher in the patients than the controls (145 ± 61 μU/ml *vs.* 43 ± 7, $p < 0.05$, Table 5). In spite of the marked hyperinsulinemia, the patients disposed of significantly less glucose than the controls (6.23 ± 0.87 mg/kg • min *vs.* 9.46 ± 0.79, $p < 0.02$). Moreover, a marked difference was observed between the two groups in the alterations in glucose disposal that occurred with time. The normal controls progressively increased the quantity of glucose cleared. In contrast, the patients demonstrated insigificant changes in glucose disposal with time (Fig. 5) in spite of progressive increases in plasma insulin (Fig. 6).

The M/I ratio has been proposed as an index of tissue sensitivity to insulin.[8] In the present study this ratio was 9.3 ± 3.3 in the patients, significantly less than the 25.0 ± 2.2 ($p < 0.001$) observed in the controls. This ratio may not adequately reflect the abnormal interrelationship between insulin and glucose disposal observed. For

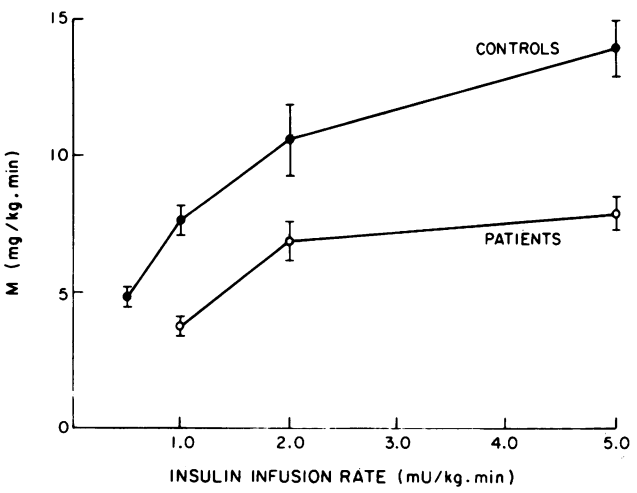

FIG. 2. Effects of insulin infusion on glucose disposal (M) during two hours of insulin infusion at various doses and euglycemia (mean ± SEM).

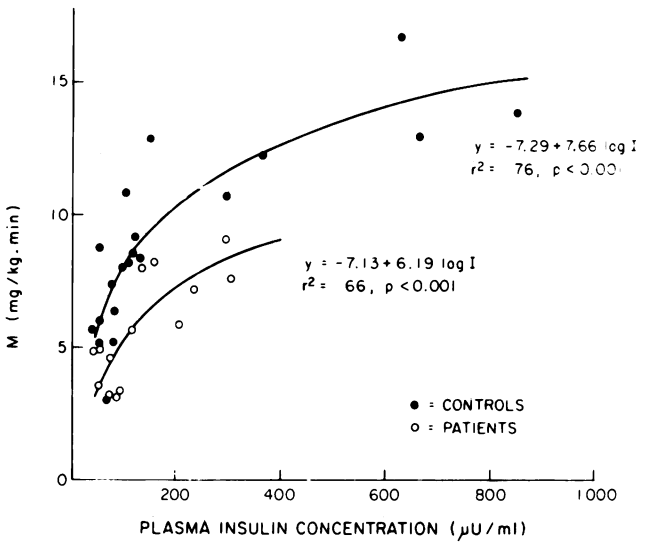

FIG. 3. Dose response plots of glucose disposal at various plasma insulin concentrations achieved during insulin infusion and euglycemia. The dose response curves are significantly different by covariant analysis ($p < 0.001$ for difference in intercept, NS for difference in slope).

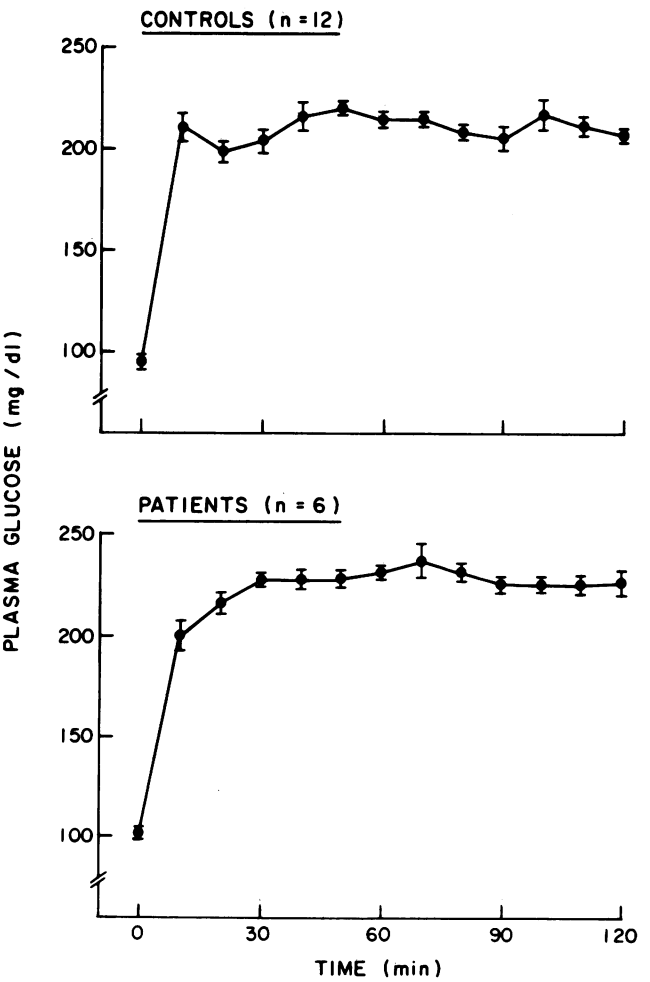

FIG. 4. Steady-state plasma glucose concentrations achieved in controls and patients during the hyperglycemic glucose clamp studies.

TABLE 5. *Results for Individual Patients—Glucose Clamp*

Patient	Basal Glucose (mg/dl)	Basal Insulin (μU/ml)	Basal Glucagon (pg/ml)	M (mg/kg · min)	Total Insulin (μU/ml)	M/I	Total Glucagon (pg/ml)	I/G
A	86	33	190	4.12	136	3.0	46	2.96
B	109	15	60	5.98	27	22.1	25	1.08
C	113	17	80	7.19	130	5.5	17	7.65
D	102	32	270	7.30	432	1.7	104	4.15
E	110	31	390	7.75	115	6.7	156	0.74
F	90	6	210	5.01	30	16.7	35	0.86
Mean ± SEM	102 ± 5	22 ± 5	200 ± 50	6.23 ± 0.87	145 ± 61	9.3 ± 3.3	64 ± 22	2.9 ± 1.1
Controls (N = 12)	95 ± 3 NS	10 ± 1 P < 0.005	108 ± 22* NS	9.46 ± 0.79 P < 0.02	43 ± 7 P < 0.05	25.0 ± 2.2 P < 0.001	23 ± 4* NS	2.3 ± 0.5* NS

* N = 8.

example, a linear relationship existed between M and insulin concentrations in the controls; as insulin concentration rose, glucose disposal increased. A similar response was not observed in the patients. In fact, over a broad range of endogenous insulin concentrations, there was little change in the glucose disposal rate (Fig. 7).

Marked glucagon suppression occurred in both groups (Table 5, Fig. 8). However, in spite of the prolonged hyperglycemia, glucagon concentrations in the patients did not decline to the levels observed in the controls suggesting insufficient suppression. Moreover, the large difference in the mean plasma insulin concentrations between groups resulted in I/G ratios that were not significantly different despite differences in plasma glucagon concentrations (Table 5).

Isotopic Studies

Mean basal endogenous glucose production was 3.40 ± 0.31 mg/kg · min in the three patients studied, similar

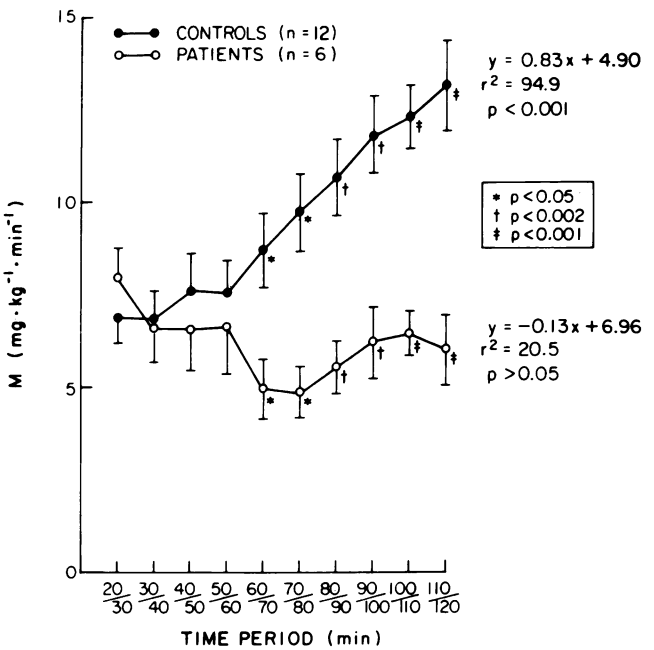

FIG. 5. With time the rate of glucose disposal (M) in the control subjects progressively increased during the hyperglycemic glucose clamp. In contrast, glucose removal was relatively constant in the patients over the two hours of the study. In the patients the infusion rate plotted *vs.* time was similar to a horizontal line. Between group responses were significantly different; differences between individual time points are noted.

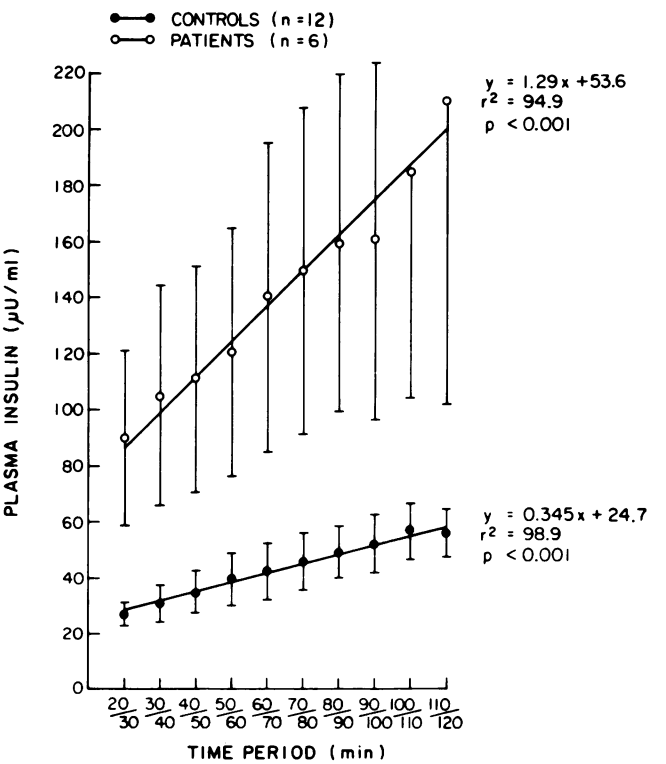

FIG. 6. Plasma insulin concentration rose during fixed hyperglycemia in both groups over the course of the study.

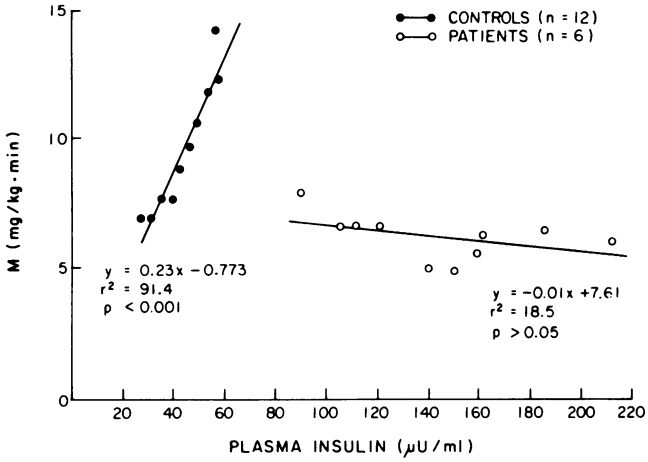

FIG. 7. In the controls, as plasma insulin rose, glucose disposal increased during the hyperglycemic glucose clamp studies. In contrast, over a wide range of plasma insulin concentrations glucose disposal did not change in the injured patients. Points shown are group means.

to results previously reported.[24] Endogenous glucose production was suppressed 38% and 75% during the hyperglycemic glucose clamp. During the euglycemic insulin clamp there was 91% suppression of endogenous production at an insulin infusion rate of 5.0 mU/kg min (Table 6).

Discussion

Alterations in carbohydrate metabolism are central to metabolic responses to injury. Glucose is a necessary and primary fuel of reparative tissue, and its synthesis occurs at the expense of both body proteins and energy stores in the traumatized patient. Glucose production is accelerated in the injured patient,[25-27] and this substrate is principally produced in the liver.[28] A major portion of the increased amount of glucose produced in the basal state is consumed by the wound and little, if any, is utilized by skeletal muscle. In previous studies[29] glucose exchange across the lower extremities was measured in nonbacteremic injured patients. Blood flow was monitored by plethysmographic techniques and arterial-venous differences of glucose and other substrates were determined across the extremity studied. In extremities with large surface burns, glucose consumption (calculated as blood flow times A-V difference) was significant, and most of the glucose consumed could be accounted for by the quantity of lactate released. In contrast, uninjured extremities consumed minimal quantities of glucose (less than 30 g/day). Thus, the body's response following injury appears to selectively direct glucose toward injured tissue to insure an ongoing nutrient source for wound repair. This is accompanied by a decrease in insulin-mediated glucose uptake in selective tissues; the primary tissues involved in insulin facilitated glucose transport are skeletal muscle, which accounts for 30 to 40% of body mass and, to a lesser extent, body fat, which comprises approximately 20 to 40% of body weight.

But what directs the flow of glucose to specific tissues? The neurohormonal environment appears to be central to the control of substrate flux, and previous studies have indicated that the flow phase of injury occurs at a time when cortisol, glucagon, and catecholamines are all elevated while insulin concentration may be normal or slightly increased.[30] In this study we directed our attention toward the body's response to insulin in order to quantitate more precisely the alterations in tissue sensitivity to this hormone. The biologic response to a hormonal stimulus can be quantitated broadly by examining two separate characteristics inherent in the tissue reacting to the stimulus.[9] The first characteristic is the sensitivity of the tissue to physiologic quantities of the hormone. The second method is the maximal response that the hormone can elicit.

In this study the euglycemic insulin clamp technique was utilized to examine the dose-response relationship between plasma insulin concentration and glucose disposal in severely injured patients. Mathematical analysis

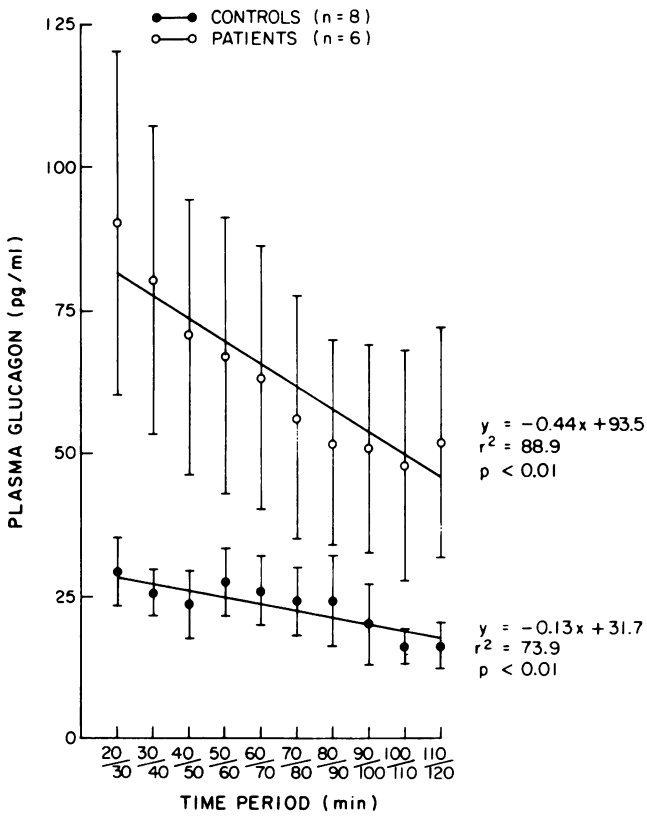

FIG. 8. Plasma glucagon concentrations are suppressed over the two hours of the hyperglycemic glucose clamp.

of this relationship using the Lineweaver–Burk transformation aided in understanding and describing the glucose kinetics involved as well as the glucose-insulin relationships. The average insulin concentrations necessary to achieve glucose uptake that was half the maximal disposal rate (a value that could be described as an apparent Km) were 85 and 86 μU/ml in the controls and patients, respectively. These values for Km are calculated from the total glucose uptake and include both insulin-mediated and noninsulin-mediated glucose disposal. However, in the basal state approximately 70% of glucose uptake in normals is not mediated by insulin.[31-33] Assuming that the uptake of glucose in the wound is noninsulin-mediated, and correcting both study groups so that only insulin-mediated glucose disposal is considered, the Km for the controls increases to 119 μU/ml and that of the patients becomes 132. These results are similar to the results for Km reported in the literature[34,35] and suggest that total body tissue sensitivity to insulin using this criteria is comparable in both study groups.

In contrast, the maximal disposal rate of glucose achieved was quite different between the two groups (Fig. 3). The maximal glucose disposal rate in the controls was 14.3 ± 0.78 mg/kg · min, a value comparable with those reported in other normal populations.[34,35] The value of 9.17 ± 0.87 for the patients was significantly less than that observed in the normal controls. The data used for these calculations are based solely upon the amount of exogenous glucose infused and do not include endogenously produced glucose. However, in normal controls the infusion of insulin at rates of 0.5 mU/kg · min or greater has been shown to suppress hepatic glucose production by more than 90–95%.[14,32] Moreover, Wolfe et al.[24] infused insulin at a mean rate of approximately 1.0 mU/kg · min into thermally injured patients and maintained euglycemia while concurrently infusing glucose at a constant rate of 4.0 mg/kg · min. This study resulted in suppression of hepatic glucose production in amounts equivalent to the suppression observed in normal controls.[24] Furthermore, in the injured patient we studied using tracer techniques in conjunction with the euglycemic clamp, there was more than 90% suppression of endogenous glucose production at an insulin infusion rate of 5.0 mU/kg · min. Thus, equating exogenously infused glucose with total glucose uptake will result in an underestimation of the total glucose disposal rate in both groups by approximately 0.2–0.4 mg/kg · min, values well within the range of the experimental error. These data would suggest, therefore, that the defect in insulin-glucose disposal kinetics following injury is characterized by decreased responsiveness to plasma insulin concentrations (*i.e.*, a postreceptor defect). In the physiologic range for plasma insulin (10–100 μU/ml), the response of the whole body to circulating insulin in the traumatized patient is quite similar to that seen in normals. This is because at the lower insulin concentrations studied, the disposal rate of glucose in controls and patients reflects the dominance of noninsulin dependent tissues which consume a greater proportion of the total glucose uptake than at higher concentrations, and differences between groups are less distinguishable. Thus, Wilmore et al.[7] reported a normal insulin-glucose disposal relationship following an intravenous bolus of glucose in thermally injured patients and found similar insulin responses to the provocative stimulus in both groups. However, plasma insulin concentrations remained within the physiologic range during the stimulated response, and never exceeded 88 μU/ml. The results of the present study would suggest that between-group differences in glucose disposal in response to insulin infusion are most apparent when plasma insulin concentrations are beyond the physiologic range and glucose disposal is near a maximum. During this situation insulin-dependent tissues comprise a greater proportion of the whole body glucose disposal, and alterations in tissue responsiveness to insulin become more apparent.

TABLE 6. *Results of Isotopic Studies*

	Basal Ra mg/kg · min.	Mean Ra During Clamp mg/kg · min.	% Suppression
Glucose Clamp (Patients)			
1	3.92	2.48	38%
2	2.84	0.72	75%
Insulin Clamp (Patients)			
1	3.45	0.30	91%

In addition to the dose response data, the euglycemic insulin clamp allowed calculation of the metabolic clearance rate of insulin (MCR_I). In this study the MCR_I for the patients was consistently higher than observed in the normals at all doses of insulin infused. These results confirm the observations of others.[24,36] In normals the major sites of insulin clearance are the liver, the kidneys, and skeletal muscle which extract approximately 47%, 25%, and 20%, respectively, of the plasma insulin flowing through these tissues.[19] Wilmore et al.[28] have previously studied hepatic and renal bloodflow following thermal injury and demonstrated that bloodflow to the liver increased almost two-fold, while renal bloodflow increased 25%. Assuming that the rate of plasma insulin extraction in these tissues remained unchanged and that alterations in blood flow in these patients were similar to those reported in the previous study, almost 80% of

the increased insulin clearance could be accounted for by the alterations in bloodflow observed in these tissues. From the practical standpoint, these data can be translated into the general rule that twice the infused dose of insulin is necessary in the trauma patient to achieve the comparable concentrations observed in normals.

The hyperglycemic glucose clamp is similar to the clinical practice of infusing hypertonic glucose for nutritional support. The response to fixed hyperglycemia was elaboration of insulin and suppression of glucagon. Yet, despite relative hyperinsulinemia, glucose disposal in the patients was significantly less than that observed in the normal controls. For these studies, M was calculated based solely on exogenous infused glucose. Previous studies[21,32,37] have demonstrated that glucose infusion rates of 2.0 mg/kg · min or above resulted in almost complete suppression of hepatic glucose production in normals; using the exogenous glucose infusion rate would, therefore, underestimate total glucose utilization by 0.3–0.5 mg/kg · min in normals. Previous glucose infusion studies in injured patient[24,38] demonstrated that endogenous glucose production is only partially suppressed; however, these measurements are difficult to relate to the present investigation. In the earlier reports the rates of exogenous glucose infused were frequently less than the endogenous glucose produced. Consequently, even if hepatic glucose production was suppressed an amount equal to the glucose infusion rate, there would not be 100% suppression of endogenous production in many of the injured patients in these reports. In the present investigation, the patients who were studied using the hyperglycemic glucose clamp while endogenous glucose production was measured, utilizing a simultaneous infusion of isotopically labeled glucose, demonstrated suppression of endogenous glucose production of 38 and 75%. If it is estimated that hepatic suppression of glucose in these patients was 50%, a value that is conservative based on both tracer[24] and arterial hepatic vein catheterization studies,[38] mean basal glucose production of these traumatized patients of 3.40 ± 0.31 mg/kg · min would be reduced to 1.70. If this amount is added to the disposal rate for each patient, the "corrected" M would approach the 95% confidence limits of the M value observed in the normal controls. However, Figures 5 and 7 illustrate that M does not correlate to either time or plasma insulin concentrations in the injured patients. In contrast, the normal controls showed a strong correlation between glucose disposal, time of infusion, and plasma insulin concentration. These data suggest that a qualitative as well as a quantitative difference exists in the response of traumatized patients to fixed hyperglycemia when compared with normals. Adding the presumed contribution of endogenous glucose production to mean glucose disposal would not alter qualitative differences between groups. Moreover if fixed hyperglycemia is maintained for four hours, the glucose disposal rate in the patients remains relatively constant while the controls continue to increase glucose disposal and plasma insulin concentration (unpublished observations). These data demonstrate that the normal response to fixed hyperglycemia is characterized by a rising insulin concentration and increasing glucose disposal. In contrast, injured patients achieve their maximal rate of glucose disposal soon after the onset of hyperglycemia. This disposal rate is less than observed in normals and appears unaffected by increasing concentrations of insulin. These findings support the results of the euglycemic insulin clamp studies which indicate that a significant difference in the maximal glucose removal exists between injured patients and controls.

Another interpretation of the results from the hyperglycemic clamp study, however, is that insulin secreted by the beta-cell in trauma patients and measured by immunoassay may not consist entirely of biologically active hormone. The immunoassay technique used to determine plasma insulin concentrations in this study cannot distinguish between insulin and proinsulin, the latter of which has markedly attenuated biologic activity. If a significant amount of the measured immunoreactive insulin in these patients was in fact proinsulin or an insulin degradation product that maintains immunoreactivity, the measured plasma insulin concentrations would be spuriously increased, resulting in abnormal glucose disposal in response to glucose infusion. Alteration in the true biologic activity of the hormone secreted by the beta-cell would not, however, change the responses noted in the patients with the infusion of exogenous hormone and would not alter between-group differences.

What tissues utilize the exogenous glucose infused during hyperinsulinemia and euglycemia? During the euglycemic state, glucose consumption by the central and peripheral nervous systems, renal medulla, bone marrow, erythrocytes, and leukocytes, all tissues known to have noninsulin dependent uptake of glucose, should remain relatively fixed and should be similar to uptake in the postabsorptive state. The uptake of glucose in these tissues should be similar to that previously reported for regional glucose consumption in controls and patients studied during the basal state (Table 7).[33,39] Splanchnic uptake of glucose occurs during euglycemia. Both *in vivo*[40] and *in vitro*[41] studies demonstrate that glucose concentrations in arterial and hepatic vein blood are similar during the euglycemic hyperinsulinemic state, and net splanchnic balance is zero. Yet hepatic

glucose production, measured by isotopic techniques, is not completely suppressed. Estimating that 90% of endogenous glucose production is suppressed during euglycemic hyperinsulinemia would mean that 10% of the basal endogenous glucose is still being produced. For net balance to be zero, the splanchnic bed must consume a quantity equal to 10% of the basal endogenous glucose production. Thus, in both study groups approxiately 0.24–0.35 mg/kg • minute of glucose would be consumed by the splanchnic tissues under the experimental conditions.

In the patients the wound is a major glucose consumer and accounts for 80 to 150 g/day, depending upon the wound size.[29] Assuming that this is obligatory uptake which is not greatly increased by exogenous insulin infusion and that glucose storage does not occur in reparative tissues, this rate of glucose disposal would not be appreciably altered during euglycemic hyperinsulinemia. The primary effect of insulin is to enhance the uptake of glucose by peripheral tissues, mainly skeletal muscle and fat. Bjorntorp et al.[42,43] have demonstrated that less than 1% of an oral or an intravenous glucose load is taken up by adipose tissue. Thus, the major effect of insulin appears to be on muscle tissue, which would have a maximal glucose disposal rate of approximately 12.16 mg/kg • min in normals. This derived value that would account for approximately 80–85% of maximal glucose uptake. This fraction of total glucose disposal compares favorably with direct measurements of glucose uptake across extremities in normals during the euglycemic insulin clamp.[44] In contrast to normals, skeletal muscle glucose uptake in the patients is much lower and represents approximately one half of the quantity of glucose utilized by skeletal muscle in normals. An underestimation of the glucose consumed by visceral tissues, adipose tissue or the wound would further reduce the contribution of glucose disposal by skeletal muscle in injured patients and accentuate the insulin resistance of skeletal muscle even more. Direct measurement of glucose disposal across regional beds is now in progress to confirm these calculations.

The cause(s) of insulin resistance in skeletal muscle are unknown. As previously mentioned, the shape of the dose response curve and interpretation of the kinetic analysis of the data from the euglycemic insulin infusions support the conclusion that the failure to respond normally to insulin is due to a postreceptor, intracellular defect in glucose metabolism. Epinephrine infusion reduces skeletal muscle glucose uptake, and this effect is thought to occur at the phosphoralation step of glycolysis.[20] With increased sympathetic tone, there is catecholamine stimulated lypolysis, and free fatty acids have been proposed as a competitor with glucose as a primary fuel source, possibly causing glucose intolerance.[45] The relative role of these and other factors in the genesis of the glucose intolerance is unknown. Moreover, the interrelationship between the postreceptor hormonal defect and increased skeletal muscle proteolysis remains to be determined.

TABLE 7. *Estimated Glucose Utilization in a 70-Kg Subject During* Euglycemia at Rates of Maximal Disposal (mg/kg • min)*

	Normal	Injured Patient
Central nervous system	1.19	1.19
Kidneys	0.36	0.74
Splanchnic bed	0.24	0.35
RBC, WBC, bone marrow	0.34	†
Wound	—	0.88–1.58
Adipose tissue	0.01	0.01
Skeletal muscle	12.16	5.31–6.00
Total glucose uptake	14.30	9.17

* The values are estimates based on the maximal rate of glucose uptake as determined by the two-hour insulin clamp studies. It is not known if long-term studies would yield similar results or induce subsequent tissue changes.

† Included in wound estimate.

These data can be useful from the aspect of patient care, for the constant infusion of hypertonic glucose is a common component of most intravenous feedings in critically ill patients. The hyperglycemic glucose clamp data suggest that patients with injuries will have a maximal rate glucose uptake of approximately 6 mg/kg • min when no exogenous insulin is administered. In a 70-kg patient, this would provide about 600 g/day or 2400 glucose kcal. To avoid hyperglycemia which would exceed the normal renal tubular threshold for glucose, only two liters of "standard" central vein solution (containing 250 g of carbohydrate per liter) should be administered per day. If required, additional calories could be administered as fat emulsion. Data from the euglycemic insulin clamp studies suggest that insulin stimulation should increase the maximal rate of glucose disposal to approximately 9 mg/kg • minute, or 900 g of carbohydrate per day in a 70-kg patient. Thus, alternatively, with insulin administration three or four liters of standard solution could be given. Because of the complications recently associated with large quantities of glucose infused into hypermetabolic patients,[46,47] we would favor the lower levels of hypertonic nutrient solution infusion (2 liters/day), which would maintain energy balance in most of our study patients.

In conclusion, this study demonstrated that (1) the maximal rate of glucose disposal is reduced in trauma patients compared to controls; (2) the metabolic clearance rate of insulin in the injured patient is almost twice normal; (3) insulin resistance following injury appears

to occur in peripheral tissues, probably skeletal muscle, and is consistent with a postreceptor defect.

Note added in proof: In additional insulin infusion studies, we have achieved insulin concentrations in one patient in excess of 1,000 μU/ml. Rates of glucose disposal ranged between 8–9 mg/kg · min, confirming this limit in glucose disposal following injury, even at supraphysiologic insulin concentrations.

Acknowledgments

This work was made possible by the support of Ms. Peggy Ball and Dr. Tom Aoki and their laboratory staff, to which we extend our thanks.

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Appendix

Insulin Resistance: A state in which normal concentrations of insulin elicit less than normal responses. The response studied in these experiments was glucose transport.

Insulin resistance may be subdivided into two general categories:

1. Decreased insulin sensitivity. A relative change in the response to insulin, as characterized by a shift of the dose response curve to the right. Increased concentrations of insulin may overcome this deficit to achieve a normal maximal response.

2. Decreased insulin responsiveness. A decrease in the maximum response to insulin. Because this deficit is thought to be related to alterations in intracellular metabolism, the deficit *cannot* be overcome by administering large quanties of insulin.

Prereceptor Defect: Insulin resistance in which there is normal responsiveness to insulin but decreased sensitivity.

Postreceptor Defect: Insulin resistance in which there is normal sensitivity to insulin but decreased responsiveness.

Maximal Response: The greatest rate of glucose disposal that can be elicited regardless of insulin concentration.

Half-Maximal Response: That response midway between basal and the maximal response.

M: The rate of glucose removed from the plasma in mg/kg · min as determined in "clamp" studies. This rate is based on the infusion rate of glucose corrected for fluctuations in the plasma concentration and urinary losses. Assuming that the contribution of the endogenous glucose produced is minimal, this value is the transfer rate of glucose out of the plasma. Although M was initially defined as "glucose metabolized," it is better thought of as a rate of glucose disposal since the intracellular fate of the glucose, once removed from the plasma, is unknown.

Lineweaver–Burk Equation: A method of using reciprocal plots of dose response data obtained from enzymology experiments. Because of the ease of this approach, this method has been extended to aid interpretation of other dose response data. A double reciprocal plot of the data is made $\left(\text{In this case } X = \frac{1}{\text{Insulin Concentration}}; Y = \frac{1}{M}\right)$. The Y intercept of this plot equals $\frac{1}{V_{max}}$, and the X intercept equals $-\frac{1}{Km}$, where:

V_{max}—is the maximal quantity of glucose disposal, regardless of insulin concentration. This is synonymous with maximal response.

Km—is the plasma insulin concentration at which the half-maximal response is noted. If the maximal responses are different, the half-maximal responses are usually different. Yet, under these conditions the Km (insulin concentration for the half-maximal response) may be the same.

Discussion

DR. JOHN M. KINNEY (New York, New York): There has always been a basic problem in trying to look at the situation called "the diabetes of injury," and this is the intimate relationship between glucose and insulin which has been nearly impossible to separate. One didn't know what activity was do to one, versus the other. The beauty of the clamp technique is the fact that you can fix one, and then look at the other.

I think the authors are to be congratulated on producing data that goes a long way to resolve some of the previous conflicts and controversy. How much was insulin resistance? How much was glucose intolerance? Were they, in fact, partly the same thing?